BLA 761362

BLA APPROVAL

Sandoz, Inc.
Attention: Raheel Khan, MBA, RAC
Associate Director, Global Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Raheel Khan:

Please refer to your biologics license application (BLA) dated and received December 5, 2022, and your amendments, submitted under section 351(k) of the Public Health Service (PHS) Act for Jubbonti (denosumab-bbdz) injection 60 mg/mL for subcutaneous use and Wyost (denosumab-bbdz) injection 120 mg/1.7 mL (70 mg/mL) for subcutaneous use.

This BLA proposes that:

- Jubbonti (denosumab-bbdz) injection, 60 mg/mL single-dose prefilled syringe for subcutaneous use is interchangeable with US-licensed Prolia (denosumab) injection, 60 mg/mL single-dose prefilled syringe for subcutaneous use.
- Wyost (denosumab-bbdz) injection, 120 mg/1.7 mL (70 mg/mL) single-dose vial for subcutaneous use is interchangeable with US-licensed Xgeva (denosumab) injection, 120 mg/1.7 mL (70 mg/mL) single-dose vial for subcutaneous use.

We acknowledge receipt of your major amendment dated November 17, 2023, which extended the goal date by three months.

LICENSING

We have approved your BLA for Jubbonti (denosumab-bbdz) and Wyost (denosumab-bbdz) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Jubbonti and Wyost under your existing Department of Health and Human Services U.S. License No. 2003.

Jubbonti is indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Jubbonti reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors

for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Wyost is indicated for:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture denosumab-bbdz drug substance (DS) at (b) (4) The final formulated drug product for the single dose vial will be manufactured, filled, labeled, and packaged at (b) (4) The final formulated drug product for the prefilled syringe will be manufactured, filled, labeled, and packaged at (b) (4) You may label your product with the proprietary name, Jubbonti, and market it as a 60 mg/mL solution in a single dose prefilled syringe assembled with a needle safety device. You may label your product with the proprietary name, Wyost, and market it as a 120 mg/1.7 mL solution in a single dose vial.

DATING PERIOD

The dating period for Jubbonti and Wyost shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your

drug substance shall be [redacted] from the date of manufacture when stored at [redacted].

FIRST INTERCHANGEABLE EXCLUSIVITY

Section 351(k)(6) of the PHS Act provides:

> The Secretary shall not make approval as an interchangeable biological product effective with respect to an application submitted under this subsection that relies on the same reference product for which a prior biological product has received a determination of interchangeability for any condition of use, until the earlier of—
>
> (A) 1 year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product;
>
> (B) 18 months after—
>
> > (i) a final court decision on all patents in suit in an action instituted under subsection (*l*)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or
> >
> > (ii) the dismissal with or without prejudice of an action instituted under subsection (*l*)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or
>
> (C)
>
> > (i) 42 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has been sued under subsection (*l*)(6) and such litigation is still ongoing within such 42-month period; or
> >
> > (ii) 18 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has not been sued under subsection (*l*)(6).
>
> For purposes of this paragraph, the term “final court decision” means a final decision of a court from which no appeal (other than a petition to the United States Supreme Court for a writ of certiorari) has been or can be taken and the term “first interchangeable biosimilar biological product” means any interchangeable biosimilar biological product that is approved on the first day on which such a product is approved as interchangeable with the reference product.

Jubbonti (denosumab-bbdz) injection, 60 mg/mL for subcutaneous use and Wyost (denosumab-bbdz) injection, 120 mg/1.7 mL for subcutaneous use are the first biological products relying on their respective reference products to receive a determination of interchangeability for any condition of use. Therefore, with this approval, these products qualify as first interchangeable biosimilar biological products for purposes of section 351(k)(6) of the PHS Act. The expiration date of any first interchangeable exclusivity has yet to be determined.

For each interchangeable biosimilar biological product approved by this letter, submit a general correspondence to this 351(k) BLA informing the Agency of the date of the first commercial marketing within 30 days of such date. Submit a duplicate copy of the correspondence via email to PurpleBook@fda.hhs.gov.

If applicable, submit a general correspondence to this 351(k) BLA informing the Agency of the date of any final court decision (as defined in section 351(k)(6) of the PHS Act) on all patents in suit in any action implicating this BLA instituted under section 351(*l*)(6) of the PHS Act, or the date of dismissal with or without prejudice of any action implicating this BLA instituted under section 351(*l*)(6), within 30 days of such date or within 30 days of this approval if such date occurred prior to approval. Submit a duplicate copy of the correspondence via email to PurpleBook@fda.hhs.gov.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Jubbonti and Wyost to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Jubbonti and Wyost, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with a minor editorial revision listed below and reflected in the enclosed labeling.

- The page numbering was corrected in the Jubbonti label.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on November 2, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761362**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4551-1 Conduct a commercial-scale process performance qualification study to confirm capability and consistency of the denosumab-bbdz vial drug product (b) (4) process, controlled using the updated and approved (b) (4) Submit the study results and analyses in a final study report to the BLA.

The timetable you submitted on November 22, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2024

4551-2 Perform a supplemental method validation study using appropriate denosumab-bbdz samples containing sufficient impurities to confirm the capability of the non-reduced CE-SDS for accurate quantification of low molecular weight (LMW) species. Submit the study results, including an evaluation of accuracy, linearity, and limit of quantitation for LMW species, in a final study report to the BLA.

The timetable you submitted on November 22, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2024

4551-3 Conduct a (b) (4) validation study from a microbiology perspective for (b) (4) two additional runs (b) (4) The validation data will be provided in a CBE0 or the (b) (4) supplement.

The timetable you submitted on November 22, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2025

4551-4 Re-evaluate and tighten the endotoxin limit [redacted] (b) (4) after data from thirty denosumab-bbdz DS batches have been obtained. The endotoxin limit and supporting documentation will be submitted in the second Annual Report.

The timetable you submitted on November 22, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2026

Submit clinical protocols to your IND 135707 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Food Drug Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Jubbonti to ensure the benefits of the drug outweigh the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) including dialysis-dependent patients associated with Jubbonti.

Your proposed REMS must also include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Jubbonti is necessary to ensure the benefits of the drug outweigh the risk. The communication plan provides for the dissemination of information about the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) including dialysis-dependent patients associated with Jubbonti.

The communication plan must include, at minimum, the following:

- Dissemination of REMS Letters to healthcare providers and professional societies according to the timeframes listed in the REMS Document
- Dissemination of the Jubbonti Patient Guide via professional meetings and field-based medical representatives to be used as a patient counseling tool
- Maintain a Jubbonti REMS website with all REMS materials

Your proposed REMS, submitted on December 5, 2022, amended and appended to this letter, is approved.

The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Jubbonti into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

Outreach and Communication

1. REMS Communication Plan activities: (*Provide data for 18-month report only)
    a. *Number of Healthcare Providers (HCPs) (stratified by specialty) targeted by the REMS
    b. *Number of professional societies targeted, and which professional societies reported distribution of the REMS letter to their respective members
    c. *REMS Letters: A summary that includes the following information, stratified by distribution waves (i.e., date distributed):
        i. Total number and percentage of hardcopy **REMS Letter for Healthcare Providers** mailed, returned, and resent after obtaining correct address.
        ii. Total number and percentage of **REMS Letter for Professional Society** emails successfully delivered, opened, and unopened. Include the total number and percentage of hard copy letters mailed after undeliverable email attempts or for which the email address was unavailable.
    d. Number and specialty of prescribers who received the **Patient Guide**
    e. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed and/or distributed.

Implementation and Operations

2. Program Implementation (*Provide data for 18-month report only):
    a. *Date of first commercial availability of Jubbonti
    b. *Date when the **REMS website** went live
    c. Number of total visits and unique visits to the REMS website
    d. Number and type of REMS materials downloaded or accessed.
3. Utilization Data
    a. Jubbonti utilization information including but not limited to indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)

Knowledge

4. Evaluation of HCPs' knowledge:
    a. An evaluation of HCPs' understanding of the risk of severe hypocalcemia in patients with advanced chronic kidney disease via analysis of assessment survey results; and stratify results by HCP specialty (e.g., endocrinologist, rheumatologist, primary care provider).
    b. An evaluation of HCPs' understanding of the need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Jubbonti and stratify results by HCP specialty.
    c. An evaluation of HCPs' understanding of the requirement to give each patient a copy of the **Patient Guide** via analysis of assessment survey results.

Health Outcomes and/or Surrogates of Health Outcomes

5. Safety Surveillance:
    a. A summary and analysis of all post-marketing case reports of severe hypocalcemia associated with Jubbonti, stratified by kidney function.

Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or elements should be modified.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches,

study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

- Submit your proposed protocol for (b) (4) for FDA review within 90 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **BLA 761362 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g., **REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/SURVEY METHODOLOGIES)**

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761362 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761362
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761362
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761362
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761362
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 761362

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

If you have any questions, call Noreen Cabellon, Regulatory Project Manager, at 301-796-2899.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, MD
Director
Division of General Endocrinology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

and

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Director
Division of Oncology 1
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Jubbonti Prescribing Information
  - Jubbonti Medication Guide
  - Wyost Prescribing Information
- Carton and Container Labeling
  - Jubbonti
  - Wyost
- Jubbonti REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA E KEHOE
03/05/2024 08:01:26 AM

LALEH AMIRI KORDESTANI
03/05/2024 08:03:22 AM